PATENT APPLICATION
4115-131

APPENDIX A

Example G: Gene Therapy

Specification: The specification discloses that viruses are commonly used as vectors to introduce genes into cells by first inserting the gene of interest into the DNA of the virus and then contacting the virus with the cells. The virus then infects the cells through cell binding receptors on the surface of the virus which bind to the cells and cause the virus to be internalized by the cells. Once internalized, the virus inserts its DNA, including the gene of interest, into the genome of the cell in such a manner that the gene of interest is expressed so as to produce its corresponding protein. Applicant has discovered that if viral vectors are first contacted with the recently discovered protein algernin, the algernin complexes with the cell binding receptors on the surface of the virus, changes the conformation thereof, and increases the infectivity of the viral vector by a factor of ten. Thus, the invention relates to a complex between a viral vector and algernin and is applicable to all situations where it is desirable to introduce genes into mammalian cells with a viral vector with a higher than normal rate of infectivity. Specifically, the specification discloses that the modified viral vector can be used *in vitro* for providing desired biological action in the cells, e.g., to produce useful proteins, and, when combined with a pharmaceutically acceptable carrier in a pharmaceutical composition, *in vivo* for medicinal purposes, such as gene therapy.
The specification lists several examples of viral vectors which are candidates for use within the claimed invention. The specification also provides the amino acid sequence of algernin as well as various methods of obtaining algernin suitable for use in the invention.
The specification includes several *in vitro* working examples with representative samples of viral vectors, genes of interest, and cells demonstrating that when the viral vectors are complexed with algernin, the complex shows a higher rate of infectivity. The examples further demonstrate that the gene of interest in the infected cells is then expressed so as to produce its corresponding protein. The specification does not show any examples relating to gene therapy or any *in vivo* use of the viral vectors.

Claims:

1. A viral vector comprising:
   a virus comprising a cell binding receptor on the surface thereof
   and a gene of interest, not normally present in the virus, inserted within the DNA of the virus; and
   algernin complexed to the cell binding receptor of the virus.
2. A pharmaceutical composition comprising a therapeutically effective amount of the complex of claim 1 and a pharmaceutically acceptable carrier.
3. A method for introducing a gene of interest into a cell comprising contacting said cell with the viral vector of claim 1.

State of the Prior Art: The state of the prior art is such that using viral vectors to insert genes into cells *in vitro* is well known and is used in applications such as protein production and as a research tool.
Orkin et al., December 7, 1995, "Report and Recommendation of the Panel to Assess the NIH Investmen in Research on Gene Therapy", issued by the National Institutes of Health - This reference teaches that using viral vectors to insert genes into cells *in vivo* for therapeutic purposes, i.e., gene therapy, is highly unpredictable and undeveloped in view of the complexity of *in vivo* systems.

Analysis:

The specification discloses an *in vitro* use for the viral vector of claim 1 and clearly discloses how to make and use the viral vector in the *in vitro* environment. Since claim 1 does not recite any environment of use, only one enabled use covering the scope of the claim is needed to enable the claim. Therefore, the disclosure with respect to the *in vitro* use of the viral vector is sufficient to enable claim 1 and it would be inappropriate to include claim 1 in a rejection under 35 U.S.C. 112, first paragraph.
With respect to claim 2, the "pharmaceutical composition", "therapeutically effective", and "pharmaceutically acceptable carrier" language in combination with the fact that the only disclosed pharmaceutical use of the compositions is for gene therapy leads to the conclusion that this claim should be evaluated in terms of whether the specification teaches how to make and use the composition for gene therapy. Since the specification fails to provide any guidance regarding gene therapy, such as dosages, routes of administration, and working examples, and the state of the prior art is such that gene therapy is unpredictable and undeveloped, it would be reasonable to conclude that it would require an undue amount of experimentation to determine the therapeutically effective amounts and use the compositions for gene therapy. For the reasons set forth above with respect to claim 1, it is clear that non-therapeutic compositions

would be enabled. Since some compositions are enabled, it would be best to make a scope rejection of claim 2 using form paragraph 7.31.03.
Claim 3 is a broad claim. When read in light of the specification, it covers *in vitro* applications as well as *in vivo* gene therapy applications. Thus, claim 3 must be evaluated as to whether the specification enables the entire scope of the claim. From the above discussion with respect to claims 1 and 2, it is clear that the specification enables the *in vitro* aspects of the claim but not the *in vivo* gene therapy aspects of the claim. Therefore, it would be reasonable to make a scope rejection of claim 3 using form paragraph 7.31.03.

Rejection:

Claims 2-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabled for non-therapeutic compositions and *in vitro* uses of the viral vector of the invention, does not reasonably provide enablement for pharmaceutical compositions and their use *in vivo* for gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.
Claim 2 is directed to a pharmaceutical composition comprising a specific viral vector, the only disclosed use of the composition being *in vivo* gene therapy. Claim 3 is directed to a method which encompasses of using the specific viral vector for *in vivo* gene therapy. However, the specification fails to adequately teach how to make the composition having a "therapeutically effective amount" of the viral vector and how to use the composition and vector for *in vivo* gene therapy. Gene therapy is a highly unpredictable and undeveloped field and the skill in the art is high. See Orkin et al. which states:

> 2. While the expectations and the promise of gene therapy are great, clinical efficacy has not be definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.
> 3. Significant problems remain in all basic aspects of gene therapy.

The specification fails to disclose the intended patients, amounts of the viral vector to be administered, what amount is considered to be therapeutically effective, the route and time course of administration, the sites of administration, the intended therapeutic product, the intended disease, and the intended target organs. The specification also lacks any working examples showing that the viral vector as claimed would deliver the genes encoding the therapeutic products to the appropriate site and that the genes once delivered would be expressed sufficiently to provide adequate product to effect the desired therapy. In view of the quantity of experimentation necessary to determine the above parameters, the lack of direction or guidance presented, the absence of working examples for *in vivo* gene therapy, the breadth of the claims, and the unpredictable and undeveloped state of the art with respect to gene therapy, it would require undue experimentation for one skilled in the art to practice the entire scope of the claimed invention.
If claims 2 and 3 were limited as follows, this rejection would be overcome:
2. A composition comprising the viral vector of claim 1 and a carrier.
3. A method for introducing a gene of interest into a cell *in vitro* comprising contacting said cell with the viral vector of claim 1.

Example 5E: Peptides for Treating Obesity

Specification: The specification discloses an anti-obesity peptide having the following amino acid sequence:
1 5 10 15
Phe Ile Gly His Thr Ser Xaa Thr His Glu Xaa Phe Ala Thr Xaa Trp Glu Leu Leu (SEQ ID NO 1).
Where:
Xaa at position 7 is Gln, Ile, or Met;
Xaa at position 11 is Asp, Gln, or Glu; and
Xaa at position 15 is Ser or Pro.
Preferably,
Xaa at position 7 is Ile;
Xaa at position 11 is Glu; and
Xaa at position 15 is Ser.
The specification also discloses a pharmaceutical formulation comprising the peptide of SEQ ID NO 1 and a pharmaceutically acceptable carrier, diluent, and/or excipient, as well as a method of treating obesity by

administering the peptide of SEQ ID NO 1 to an obese mammal, such as mice or humans. Several routes of administration are disclosed but no dosages, not even general ranges, are disclosed.
The specification states that the peptide can be made by recombinant DNA technology or well known peptide synthesis procedures. Furthermore, the specification lists DNA sequences, vectors, host cells, and isolation techniques suitable for producing the peptide by recombinant DNA technology as well as specific peptide synthesis techniques suitable for producing the peptide.
The application discloses but does not exemplify that the peptide is a fragment of a larger protein produced in adipose tissue. The application also discloses but does not exemplify that the peptide is able to control body weight gain in normal and obese subjects. The specification discloses that suitable test animals include normal mice and obese mice, especially the ob/ob mouse model of obesity and diabetes, which is disclosed as being generally accepted in the art as being indicative of the obesity condition. The specification discloses how to carry out the animal model tests but fails to disclose whether such tests were done using the peptide of the invention. The specification also goes on to state that the peptide is also useful in the production of antibodies for diagnostic use and, as a peptide, is useful as feed additives for animals.

Claims:

1. 1. A peptide consisting of the sequence

   1 5 10 15
   Phe Ile Gly His Thr Ser Xaa Thr His Glu Xaa Phe Ala Thr Xaa Trp Glu Leu Leu (SEQ ID No. 1), wherein
   Xaa at position 7 is Gln, Ile, or Met;
   Xaa at position 11 is Asp, Gln, or Glu; and
   Xaa at position 15 is Ser or Pro.

1. The peptide of claim 1 wherein Xaa at position 7 is Ile; Xaa at position 11 is Glu; and Xaa at position 15 is Ser.
2. A pharmaceutical composition comprising the peptide of claim 1 and a pharmaceutically acceptable carrier.
3. A pharmaceutical composition comprising the peptide of claim 2 and a pharmaceutically acceptable carrier.
4. A method of treating obesity, which comprises administering to a mammal in need thereof the peptide of claim 1.
5. A method of treating obesity, which comprises administering to a mammal in need thereof the peptide of claim 2.

State of the Prior Art: There are no structurally similar peptides known in the art for treating obesity. There are other proteins that the art suggests play a role in obesity. The following references establish the state of the art with respect to such proteins.
Zhang et al, Nature, Vol. 372, pp. 425-432, December 1994.
Rink, Nature, Vol. 372, pp. 406-407, December 1994.
Marx, Science, Vol. 266, pp. 1477-1478, December 1994.
It is well established in the art how to use proteins and peptides as additives in animal feed.

Analysis:

The specification clearly teaches how to make all the peptides and compositions encompassed by the claims. Therefore, "how to make" is not an issue with any of the claims.
With respect to claims 1-2, the fact that the specification discloses that the peptides can be used as an additive to animal feed in combination with the fact that it is well established in the art how to use proteins and peptides as additives in animal feed leads to a conclusion that the specification also teaches how to use the entire scope of peptides recited in claims 1-2. Since no specific use is recited in these claims, one enabled use that covers the full scope of the claims is sufficient to preclude an enablement rejection of a compound claim based on the failure to teach "how to use".
With respect to claims 3-4, the "pharmaceutical" and "pharmaceutically acceptable carrier" language in combination with the fact that the only disclosed pharmaceutical use of the compositions is for treating obesity leads to the conclusion that these claims should be evaluated in terms of whether the specification teaches how to use the compositions for treating obesity. Since method claims 5-6 must be evaluated in

terms of the recited use, treating obesity, claims 3-6 should be evaluated together. In this case, the art noted above teaches that few medical problems have proved to be more intractable than obesity (Marx). Furthermore, even though other proteins are suggested as playing a role in obesity (Zhang), the art, such as Rink and Marx, suggest that it is not even known how to use these proteins for treating obesity. This state of the prior art suggests a lack of predictability in this art which, taken with the fact that there is a lack of guidance with respect to dosages and a lack of working examples, leads to the conclusion that it would require undue experimentation to use the invention of claims 3-6. With respect to claims 3-4, it is also noted that if the "pharmaceutical" and "pharmaceutically acceptable" language was deleted from the claims, the analysis would be the same as that set forth above with respect to claims 1-2. Therefore, an enablement rejection using form paragraph 7.31.02 of claims 3-6 would be appropriate along with a suggestion to remove the "pharmaceutical" and "pharmaceutically acceptable" language from claims 3-4 to overcome the rejection with respect to these claims.

Rejection:

Claims 3-6 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertain, or with which it is most nearly connected, to use the invention.

Claims 3-6 recite pharmaceutical compositions and methods of treating obesity using certain specific peptides. However, the specification fails to disclose any dosages for use in treating obesity. Furthermore, while the specification sets forth tests for assay anti-obesity activity of the peptides, the specification fails to provide any indication that such tests were done. Therefore, the specification also fails to provide any working examples. Marx states that few "medical problems have proved to be more intractable than obesity" and even though other proteins are suggested as playing a role in obesity (Zhang), the art, such as Rink and Marx, suggest that it is not even known how to use these proteins for treating obesity and that there is much more to be done before obesity can be treated using such proteins. In view of the intractable nature and unpredictability of treating obesity and the lack of guidance with respect to dosages and the lack of working examples, one skilled in the art could not use the inventions of claims 3-6 without undue experimentation. Note, removing "pharmaceutical" and "pharmaceutically acceptable" from claims 3-4 would overcome the rejection of these claims since one would know how to use such compositions as additives in animal feed as disclosed in the specification.

Modifications to the Above Facts: Let us assume that in addition to the above facts, the specification actually stated "The disclosed animal model assays were carried out using the peptides of the invention and the peptides were active in at least one of the assays. Therefore, the peptides are useful in treating obesity and those disorders implicated by obesity." Does this change the analysis set forth above? For claims 1-2, the answer is no. For claims 3-6, the answer is yes. Specifically, if the assays are reasonably correlative to treatment in other mammals such a statement would constitute the presence of working examples, even without the specific data. In this case, since specific dosages are not disclosed generally or in the examples, the only issue remaining is whether it would require an undue amount of experimentation to determine the proper dosages based on the examples and the state of the prior art and any enablement rejection must address this issue. If the assays do not reasonably correlate to treatment in other mammals based on the state of the art, this issue would have to be raised along with the other issues noted in the analysis and rejection above.

Note, taking the position that the assays are reasonably correlative to treatment in other mammals, it is proper to accept as being true the statement that the peptides were active in the assays, even in the absence of specific data. The Office must accept as being true the statements supporting enablement unless there is an objective reason, usually supported with documentary evidence, to question them, i.e., the burden is on the Office to demonstrate that there is an objective reason, usually supported by documentary evidence, to question the statement. Here, there is no evidence indicating that the peptides were not active in the assays. However, this analysis does not necessarily apply to other issues, such as a showing of unexpected results so as to overcome a rejection under 35 U.S.C. 103. In that case, a statement that the assays demonstrated unexpected results for the inventive peptides, in the absence of the specific results, would not be persuasive since it is applicant's burden to rebut the prima facie case of obviousness and the Office cannot determine whether applicant has met that burden without the results being present.